FACT SHEET - ADENOVIRUS DISEASE CONTROL
January 2000

1. Adenovirus vaccine has been used successfully to prevent adenovirus-related acute respiratory disease in military recruit training since 1971. The manufacturer of this vaccine ceased production in 1996, and the remaining supply of vaccine was depleted in early 1999. Even if a new manufacturer is identified promptly, it will likely be several years before the adenovirus vaccine supply is reestablished. In the interim, adenovirus-related ARD rates are expected to increase, and military medical staff must be prepared to respond to this challenge.

2. Please ensure the contents of this document are disseminated to Preventive Medicine, Family Practice, Primary Care, Services, Clinics, and Sections and command unit surgeons involved with recruit training units. Even though instituting the non-vaccine adenovirus interventions as outlined in this document may not prevent adenovirus epidemics, following the recommendations will help prepare for and help manage any outbreak of adenovirus infections.

3. Historical Aspects

a. Soon after the discovery of adenoviruses in 1953, it was determined that these pathogens were an important cause of acute respiratory disease (ARD) among military personnel, especially among recruits. By the 1960s, The Commission on Acute Respiratory Diseases of the U.S. Armed Forces recognized that adenoviruses were the principal cause of ARD epidemics of among military recruits. At times, as many as 80% of new military recruits were affected by ARD within the first 3 weeks of training. Of these, perhaps 20% required hospitalization.

b. Vaccine Development. In the mid 1960’s an efficacious, acceptable adenovirus type 4 vaccine was developed. However, adenovirus type 4 vaccine alone did not adequately control all adenovirus-related ARD. By 1971, adenovirus types 4 and 7 vaccines were available and found to be efficacious when given together. Originally given only during the ARD (winter) season, in 1983, Army and Navy began giving types 4 and 7 vaccines throughout the year. Routine administration of the adenovirus types 4 and 7 vaccines resulted in a substantial reduction in adenovirus-related ARD rates in military recruits.

c. Vaccine Discontinuance. In the early 1990’s Wyeth-Ayerst (the sole manufacturer) informed DoD that they would be closing their facilities because of compliance concerns with the Food and

Drug Administration (FDA), the Environmental Protection Agency, and the Occupational Safety and Health Agency. In the spring of 1996, Wyeth-Ayerst delivered for the last time, a one-year supply of adenovirus type 4 and 7 vaccines to DoD, and proceeded to dismantle their production facility. In the summer of 1997 the FDA extended, by 1 year, the expiration date of expiring vaccines based on real-time potency tests. In August 1998, Wyeth informed the Defense Supply Center of Philadelphia (DSCP) that there would be no extension of adenovirus type 4 vaccine's expiration date due to deterioration of the enteric coating. DSCP also projected at the time that adenovirus type 7 vaccine supplies would run out by Feb 1999.

d. Vaccine Line Restart Status as of December 1999. US Army Medical Research and Materiel Command (USAMRMC) has the lead for re-acquiring adenovirus vaccines. Several vaccine producers responded to an initial solicitation for interest that appeared in the Commerce Business Daily several months ago. One month ago, a team from USAMRMC visited Wyeth, at which time the company affirmed that they would not be re-engaging, but that they would provide information to USAMRMC and to the selected manufacturer. Wyeth indicated that the cost of facility that met good manufacturing practices might be considerably more than DoD currently has available for this effort. Obtaining the expertise to "tablet" the vaccine will be an additional challenge. A Request for Proposals (RFP) will be published soon. USAMRMC hopes that one or more of the manufacturers who expressed interest and perhaps others will respond to the RFP. Procurement of adenovirus vaccine may take several years longer than initially anticipated.

e. Expected Epidemic.

(1) In preparing for an expected adenovirus-related ARD epidemic the DoD made the following responses to the loss of the manufacturing of the vaccine. An adenovirus immunization policy modification, 10 Sep 96, restricted the use vaccine to 1 Sep-31 Mar, instead of year-round. This gave DoD vaccine coverage for 2-2.5 more seasons. A shelf-life extension of the existing vaccine was accomplished as noted above.

(2) After the policy for the cessation of the summer vaccinations, there was evidence of increased adenovirus type 4 infection rates among recruits at Ft. Jackson (Oct 1997 and Oct-Nov 1998), and among AIT students at Ft. Gordon. In addition recruits at the Great Lakes Naval Training Center experienced adenovirus type 7 outbreaks in the fall of 1997. More recently, adenovirus type 4 infections have been detected at Ft. Sill, OK and among Air Force training recruits at Lackland AFB, TX in 1999.

4. Clinical Aspects

a. Clinical Presentation.

(1) Infections with adenoviruses have been associated with a variety of disorders that usually affect the respiratory, gastrointestinal, and ocular systems. The infections can present as common respiratory disease, acute respiratory disease (ARD), epidemic keratoconjunctivitis, pharyngoconjunctival fever and pneumonia. These infections can occasionally be fatal in military recruits.

(2) Adenoviruses are divided into 47 serotypes based on neutralization with type-specific antisera directed against antigenic sites in the virion's hexon protein. These serotypes are grouped together by virtue of species of red cells they agglutinated and nucleic acid homology. Adenoviruses of different types behave epidemiologically in very different fashions, so that such identification is of great importance, especially when outbreaks are being investigated. The epidemic adenovirus-related ARD infections of military recruits are caused mainly by adenovirus serotypes 3, 4, 7, 14, and 21.

(3) The adenovirus-related ARD infections produce typical upper respiratory tract and constitutional symptoms. In some instances, infections may extend to the lungs with a prolonged and extensive course. In the absence of vaccination, the incubation period of ARD is usually 5 to 10 days, with the gradual development of a variety of respiratory disease symptoms beginning with fever and chills. Clinical characteristics also include sore throat, cough, headache, and chest pain. Pulmonary infiltrates in chest x-ray have been found in less than 10% of those with typical illness. The duration of infectivity is short; the virus is not demonstrable in the respiratory tract after 4 days of illness. Routes of infectivity for the adenoviruses include direct contact and aerosolized droplet transmission (aerosolized virus inhaled into the lungs).

b. Diagnosis.

(1) Establishment of a definitive diagnosis of an adenoviral infection may be impossible unless a laboratory is available with personnel experienced in handling this group of agents. Positive laboratory diagnosis is achieved by one of two procedures. The first is direct detection in clinical specimens, which uses several methods. The second procedure is isolation of the virus in cell cultures of human origin. Because it is important to diagnose a viral infection quickly and accurately,

research in this area is ongoing, with newer methods being developed.

(2) Serological diagnosis is performed using the acute-phase and the convalescent-phase (collected at 2 to 4 week intervals). It is critical to take the acute-phase serum early in the illness (i.e., within the first 5 days of illness).

(3) The Naval Health Research Center (NHRC), San Diego, and collaborators from 9 other commands are conducting clinical epidemiological surveillance that will measure the distribution of adenovirus serotypes in military trainee populations at 8 U.S. military training sites: Naval Recruit Training Center, Great Lakes, IL; Marine Corps Recruit Depot, San Diego, CA; Marine Corps Recruit Depot, Parris Island, SC; Coast Guard Training Center, Cape May, NJ; Fort Jackson, Columbia, SC; Fort Leonard Wood, Waynesville, MO; Fort Benning, Columbus, GA; and Lackland Air Force Base, Lackland, TX. Viral throat cultures are taken from trainees who visit a medical clinic and meet a broad case definition for acute respiratory disease: oral temperature of $\geq$ 100.5° F, and either cough or sore throat. Specimens are shipped on dry ice to the laboratory at NHRC, where microbiologists isolate and subtype the adenoviruses.

c. Treatment. There is no specific treatment for adenovirus infections. Indiscriminate use of antibiotics is to be discouraged; they should be reserved for patients with Group A streptococcal pharyngitis and for patients with identified bacterial complications such as otitis media, pneumonia or sinusitis. Cough medicines, decongestants, and antihistamines are only palliative.

5. Expected Morbidity And Mortality.

a. Where. The increased rates of adenovirus-related ARD have historically been associated with new military recruits at basic training installations.

b. In a 1992 DoD sero-prevalence study, in a random sample of 303 new recruits, 66% and 73% of trainees were susceptible to adenovirus types 4 and 7 respectively (consistent with sero-surveys in the 70’s). Nearly 90% were susceptible to at least 1 serotype. In a subsequent investigation at Ft. Jackson conducted in the Fall 1997, 78-85% of Army recruits were found to be susceptible to adenovirus type 4.

c. Without the adenovirus vaccine, Army recruits are now as vulnerable as in the 1960’s and 70’s for adenovirus infections. Adenovirus-related ARD is an important cause of morbidity, second

only to influenza. Deaths from the adenovirus-related ARD have been rare but they do occur. Of great concern to the military is the high attack rate over a short period of time and the incapacity that results (2-3 days of hospitalization per case).

d. The morbidity rate in U.S. military personnel in the past has reached 6 to 17 per 100 recruits per week, with 10% of the infected recruits developing pneumonia. This pattern is usually observed in the winter months.

6. Personal And Collective Protective Measures.

a. Non-vaccine acute respiratory disease interventions (NOVARDI) are available. Those administrative NOVARDI that are probably effective are listed below:

(1) Hand Washing. Literature review documented hand washing to reduce nosocomial and enteric infections, but not proven for respiratory diseases. The Navy initiated a “Stop Cough Program” in FY96 at Great Lakes. It included mandatory handwashing, 5 times daily, education on handwashing for recruits and trainers, mandatory liquid soap in barracks, and hygiene as part of personnel inspections. The program was associated with a marked (45%) reduction in overall respiratory illness rates, when vigorously enforced. Hand washing appeared to attenuate, but did not prevent, the ARD outbreak the fall of 1997

(2) Bunk Spacing. Provide minimal space between bunks for sleeping layout, AR 415-50 requires 72 sq. ft of net floor space (bed, locker, and circulation but excludes lounges, bathrooms, general circulation, halls and stairwells) per recruit. Double bunking may decrease the separation between sleeping recruits because of the vertical separation and is already being used in many of the installations. Compliance will be determined by existing buildings, building designs, and unit training sizes.

b. Other administrative NOVARDI that have been suggested in the literature, but have no proof of benefit are below:

(1) Cohorting. Hospitalized patients are already cohorted, but mildly sick patients are difficult to identify. Some have proposed cohorting as a unit for all those who become sick or are symptomatic, but problems with training schedules and cadre non-acceptance has made this operationally unacceptable. Also, mixing in auditoriums, waiting lines, classrooms, cafeterias, and buses may disrupt the cohorting effect.

(2) Sleeping head-to-toe. Already being done universally at Ft. Jackson, even though this method has not received a rigid test. It is based on the assumption that transfer of respiratory infections occurs chiefly in barracks. But it is difficult to enforce, and doesn’t address daytime congregating. There are similar problems with shelter halves as screens or sneeze sheets, and this may be a tough sell to cadre.

(3) Anti-microbial hand wipes. The use of iodinated tissues, while not preventing disease directly or ameliorating disease, may decrease the hand-to-hand or hand-to-fomite spread of disease.

c. Therapeutic NOVARDI. The use of benzathine penicillin (bicillin®), zinc lozenges, multi-vitamins, and high doses of vitamin C have been used in the treatment of other viral infections, but the evidence is sparse and much less compelling in adenovirus infections and not recommended. When bicillin® was routinely given in the reception station the ARD rates at Fort Leonard Wood were lower than "expected." While this prophylaxis was aimed mainly at the bacterial component of ARD, there may be a beneficial effect on the adenovirus infection incidence through an incompletely understood interrelationship. Carefully controlled studies of bicillin® prophylaxis are necessary in order to more accurately assess its efficacy in the treatment of adenovirus-related ARD.

d. Engineering NOVARDI that have been mentioned in the literature include: 1) dilution of indoor air; 2) UV light in air ducts (may be of benefit in preventing transmission inter-floor or inter-unit but not within the floor or the people in the same rooms); 3) control of indoor temperature and humidity (manipulation of temperature and humidity may exacerbate other respiratory diseases); and 4) the use of different building designs (may be of benefit, but would take too much time and cost too much money). Increasing air exchanges and frequently changing air filters (every 2 to 3 weeks) may be effective in preventing inter-floor or inter-unit transmission. Oiling of floors was tried in the 1950’s and 60’s in an attempt to decrease the re-aerosolization of the viruses with dust particles but was never scientifically shown to be of benefit and may not be feasible for modern floors, carpeting, etc.

e. Use of personal protective equipment, such as masks and or cotton gloves has been considered by some, but there are compliance problems, especially when sleeping. Moreover, marketing the intervention to the cadre and the command may be problematic because of perceptions of non-military bearing and esprit-de-corps.

7. Countermeasures and Preparation

a. By Training Personnel. During an outbreak, the training community may be requested to emphasize general hygiene efforts among staff and recruits, and reduce recruit crowding as much as possible. In an extreme ARD outbreak, the training community may have to be prepared to supplement staff, open more barracks spaces, or even delay the acquisition of new accessions in order to decrease crowding.

b. By Military Treatment Facility (MTF) Personnel. An outbreak should be defined when the incidence of ARD at a specific post or installation exceeds 1.5 cases per 100 recruits per week, or whenever there is a sharp upward trend from a site's baseline ARD rate. Medical staff located at training installations should consider making contingency plans for ARD outbreaks. Such plans may include:

(1) Obtaining additional medical staff (e.g., activating local reservists, requesting staff from other MTFs, or requesting increased staff resources from their Regional Medical Command or MEDCOM).

(2) Securing additional clinic space and resources to see ARD patients.

(3) Securing additional hospital space and resources for very ill ARD patients (e.g., setting up for an expanded ARD ward capability).

(4) Promptly reporting the outbreak within the preventive medicine community, and requesting assistance with pathogen identification and controls efforts.

(5) Alerting the military recruit training community to implement efforts to reduce ARD transmission, i.e., enforced hygiene and handwashing, and avoiding over crowding.

c. Surveillance Vigilance And Emphasis

(1) Weekly surveillance for ARD should be considered the most critical step in addressing the adenovirus challenge. Prompt, accurate tracking of ARD rates allows health professionals to see when outbreaks are beginning, and to assess the effects of any intervention measures. Appropriate adenovirus surveillance should include tracking of general ARD, as well as sampling for specific pathogens among hospitalized ARD cases.

Two historical references that can be used for guidance in setting up a surveillance program include:

(a) MEDCOM Memorandum, 25 Jan 1995, SUBJECT: Acute Respiratory Disease (ARD) and Adenovirus Surveillance Programs.

(b) OTSG Memorandum, 27 Dec 1989, SUBJECT: 1989-1990 Acute Respiratory Disease (ARD) Surveillance Program.

(2) The importance of ARD surveillance cannot be overemphasized. Medical staff at training installations must ensure that reporting is timely and accurate each week. Senior staff should monitor rates graphically, and interpret any increasing or decreasing trends. Assistance can be obtained in data interpretation from preventive medicine professionals at the Directorate of Epidemiology and Disease Surveillance, U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM), as well as the Naval Health Research Center (NHRC). Although data should be monitored closely on site, the training installations may compare ARD rates with each other on NHRC's emerging illness website, http://pc176.nhrc.navy.mil/disease/ilirates.htm#top.

(3) Medical and line personnel at all levels are encouraged to utilize the Defense Medical Epidemiology Database (DMED), which is a remote access application providing access to selected data contained within the Defense Medical Surveillance System (DMSS). DMSS is an automated information system that provides surveillance and epidemiological information, such as the incidence of various diseases at installations. To access DMED:

(a) Go to the Army Medical Surveillance Activity (AMSA) website: http://amsa.army.mil/AMSA/amsa_home.htm.

(b) On the left sidebar, click once on "DMED".

(c) Click on "Registration" and fill out the registration form. In 1-2 days you will receive a password.

(d) After receiving the password download the DMED application and follow further instructions.

8. The points of contact on this issue are COL Withers, Office of The Surgeon General, Department of the Army, DSN 761-3160 or Commercial (703) 681-3160, or LTC Lovell, U.S. Army Center for Health Promotion and Preventive Medicine, DSN 584-2464 or Commercial (410) 436-2464.